Compressibility and compactibillity of roller compacted materials

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Preface

This dissertation has been submitted to the University of Copenhagen in order to meet the requirements for obtaining the Ph.D. degree.

The experimental work took place from May, 2004 to December, 2006 at the Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen and at Nycomed. Within Nycomed, experiments have been performed at the International Pharmaceutical Affairs in Roskilde and at the production sites in Grenaa and Hobro.

The dissertation will be defended at the Faculty of Pharmaceutical Sciences, University of Copenhagen.

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Furthermore, I would like to thank past and present colleagues of the pharmaceutical technology group at the Department of Pharmaceutics and Analytical Chemistry for providing help, good working environment and amusing company.

Copenhagen, 2008

Charlotte Bacher

List of publications

This thesis is based on the following papers and manuscript, which are referred to in the text by the roman numerals I-IV.

I Bacher, C; Olsen, P.M; Bertelsen, P; Kristensen, J; Sonnergaard, J.M., 2007. Improving the compaction properties of roller compacted calcium carbonate. Int. J. Pharm. 342, 115-123.

II Bacher, C; Olsen, P. M; Bertelsen, P; Sonnergaard, J.M., 2008. Granule fraction inhomogeneity of calcium carbonate/sorbitol in roller compacted granules. Int. J. Pharm. 349, 19-23.

III Bacher, C; Olsen, P. M; Bertelsen, P; Sonnergaard, J.M., 2008. Compressibility and compactibility of granules from wet and dry granulation. Int. J. Pharm. 358, 69-74.

IV Bacher, C; Olsen, P. M; Bertelsen, P; Sonnergaard, J.M., 2008. Mechanical stability testing of tablets produced from sugar and sugar alcohols. Manuscript.

Table of content

1. Summary

1.1 Summary in English

Recently, an increasing interest for roller compaction has reappeared in the pharmaceutical industry. Roller compaction is a cheap and effective dry granulation process, especially applicable for voluminous powders due to powder densification. Granules for pharmaceutical application are primary produced for further compression into tablets; however, most published research in this field is mainly concerned the granule characteristics and less about the compression properties. Therefore, it is of great importance to gain more knowledge of the compression properties of roller compacted granules.

The overall aim of this project was to quantify compressibility and compactibility of roller compacted granules, composed of a bulky model substance, calcium carbonate. In order to optimize granule compactibility and thereby the tablet quality, different morphologic forms of calcium carbonate and different particle sizes of sorbitol were applied.

The compression behaviour has been explained by mechanisms including fragmentation (destructive), elastic (recoverable) and plastic (permanent) deformation. These deformation characteristics have been quantified by flexure testing, indentation methods and by studying the surface area during compression. The compressibility is defined as the ability of a powder bed to be reduced in volume due to the application of a given pressure. Own findings has been evaluated by the Walker model i.e. as the specific volume as a function of the logarithmic compaction pressure. This model has shown to possess a better

curve fitting ability and an improved discriminative power than the popular Heckel equation.

The mechanical strength of a tablet has been derived from compression, tension and indentation methods of which the most widely applied technique is by far the diametral compression test. This test has been applied for estimating the compactibility in the experimental work of this project. The compactibility is defined as the ability of a powder bed to form a mechanical resistant tablet as function of a given pressure.

The mechanical strength of dry granulated materials has been studied widely in relation to changes in process parameters of the roller compactor. The roller compaction process of brittle materials had a tendency to be more robust in regard to mechanical strength of tablets than plastic deforming materials. This is probably as a result of the formation of new surface during fragmentation, enabling new interparticulate bonds. In own findings, the morphology of calcium carbonate and particle size of sorbitol were more influential on the compaction properties than the settings of the roller compactor. In general, increasing surface area due to changes in morphology and particle size enhanced the compression- and compaction properties.

In comparison to the corresponding direct compressible blends, the compaction properties of the dry granulated materials were decreased significant. It is hypotized that the roller compacted granules are covered with the weakest bonding area on the granule surface as a result of the grinding process which splits the ribbon in the weakest links. Accordingly, the non - uniform allocation of the interparticulate attractive forces in a tablet is causing a lowering of the compactibility of roller compacted granules.

1.2 Resumé på dansk

For nylig er der opstået en stigende interesse for valsepresning i den farmaceutiske industri, da det er en billig og effektiv tørgranuleringsmetode. Den er især anvendelig for voluminøse pulvere, idet materialet bliver komprimeret og reduceret i volumen. Granulater til farmaceutisk anvendelse er hovedsagligt produceret til at blive komprimeret til tabletter. Alligevel omhandler det meste af den publicerede forskning på dette område granulatkarakteristika og i mindre grad komprimeringsegenskaberne. Derfor er det vigtigt at opnå mere viden om komprimeringsegenskaber af valsepressede granulater.

Projektets overordnede formål var at kvantisere kompressibilitet og kompaktibilitet af valsepressede granulater bestående af en voluminøst model substans, calciumkarbonat. For at optimere kompaktibiliteten af granulater og dermed tabletkvaliteten, blev forskellige morfologiske former af calciumkarbonat og forskellige partikelstørrelser af sorbitol anvendt.

Komprimeringsforløbet har været forklaret ved mekanismer som inkluderer fragmentering (destruktivt), elastisk (reversibelt) og plastisk (irreversibelt) deformation. Disse deformationskarakteristika har været kvantiseret ved bøjning, indtrængning og ved at studere overfladearealet under komprimering. Kompressibiliteten er defineret som et pulvers egenskab til at blive reduceret i volumen under trykpåvirkning. Egne resultater er blevet evalueret med Walker modellen dvs. som det specifikke volumen som funktion af det logaritmiske komprimeringstryk. Denne model har vist sig at være mere velegnet end den populære Heckel ligning til at tilpasse sig et kurveforløb og har endvidere vist en forbedret diskrimineringsevne.

Den mekaniske styrke af en tablet har været afledt fra komprimerings-, træk- og indtrængningsmetoder, hvoraf den mest anvendte teknik er den diametrale

komprimeringstest. Denne metode har været anvendt til at estimere kompaktibiliteten i det eksperimentale arbejde af projektet. Kompaktibiliteten er defineret som et pulvers egenskab til at forme en mekanisk resistent tablet som funktion af et givet tryk. Den mekaniske styrke af tørgranuleret materialer har været studeret meget i relation til ændringer af valsepressens procesparametre.

Valsepresning af skøre materialer har en tendens til at være mere robust med hensyn til mekanisk styrke af tabletter end plastiske materialer. Dette kunne tænkes at skyldes dannelsen af nye overflader ved fragmentering, hvilket giver mulighed for at danne nye interpartikulære bindinger. I egne resultater har morfologien af calciumkarbonat og partikelstørrelsen af sorbitol større indflydelse på komprimeringsegenskaberne end valsepressens indstillinger.

Generelt blev komprimerings- og kompakteringsegenskaberne forbedret af et stigende overfladeareal som følge af morfologi og partikelstørrelse. I forhold til den tilsvarende direkte komprimering af blandingerne er komprimeringsegenskaberne af de tørgranulerede materialer blevet forringet signifikant. Det forestilles at de valsepressede granulater er dækket med de svageste bindingsområder på granulatoverfalden som et resultat af sigtningsprocessen som bryder kompaktet i de svageste bindinger. Derfor er de interpartikulære tiltrækningskræfter i en tablet af tørgranulater fordel skævt, hvilket medfører et fald i kompaktibilitet af valsepressede granulater.

2. Introduction

2.1 Background

The tablet is the most common pharmaceutical dosage form; thus the formulation and processing of tablets are of great interest in the pharmaceutical development and manufacturing. A great focus lies on creating processes, which generate tablets meeting the specified quality requirements in accordance to the regulations. Problems due to a complicated process cost time and money. Therefore it is advantageous to have more knowledge in choosing suitable starting materials and a feasible tablet manufacturing process.

Compression of an active pharmaceutical ingredient (API) with direct compressible excipients is preferable, however it is general only possible if the API has similar physical properties as the excipients and it possesses good flow- and compression properties. Consequently, in order to prevent demixing of bulk materials and avoid large dose variation, granulation is often indispensable as it transforms powdery materials into larger agglomerates improving flow properties. Traditionally, wet granulation in batch scales is applied because the equipment and expertise are well known and available. In wet granulation, a liquid binder is distributed onto a powder blend in motion and subsequently the granules are dried. Lately, an increasing interest for the continuous dry granulation process; roller compaction has reappeared. In dry granulation, a powder blend is compressed into a compact which is ground in order to form granules. This fairly simple and liquid free granulation have some advantages over the wet granulation methods as the roller compaction is a cheap and cost efficient process which is applicable for moisture and heat sensitive

formulations. On the other hand, the roller compaction produces a relative large amount of fines and it reduces the compaction properties of the starting materials.

Despite the fact that most granules are compressed into tablets, a lot of research is going on in the field of granulation in which the compaction behaviours of granules are paid less attention. Instead of focusing on less relevant granule properties, it is extremely important to quantify the compaction properties as it is a direct measurement of the granule characteristic. Moreover, compression affects critical tablet quality aspects as the mechanical strength, disintegration- and dissolution rate. It is required that a tablet possess a sufficient mechanical strength in order to avoid disintegration of the tablet during handling as well as assuring that the API dissolute on time.

In pharmaceutical powder technology, a distinction is made between the consolidation characteristics of powders: The compactibility and the compressibility. The compactibility is the ability of a powder bed to form a mechanical resistant tablet; it's usually described in terms of the mechanical strength as a function of applied compaction pressure (Leuenberger, 1982). The mechanical strength is a direct measurement of the product quality and it is normally monitored as an in process control in tablet productions. However, the mechanical strength often changes after the compression as it is affected by the tablet aging, temperature, moisture sorption and desorption (Bhatia and Lordi, 1979; Karehill and Nyström, 1990; Mollan and Celik, 1995). Therefore, commonly the storage conditions should be well defined.

The compressibility, in contrast to the compactibility, has less industrial focus as it is an implicit determination of the ability to form tablets; thus the compressibility is defined as the ability of a powder bed to be reduced in volume

due to the application of a given pressure (Leuenberger, 1982). Compression and compaction are often mistaken as synonyms in everyday use because the processes occur in a tablet press as inseparable and dependant sequences. When a powder bed is compressed, compaction often occurs though not necessarily, since the compaction requires the formation of interparticulate bondings in order to form a coherent tablet.

Among crystalline APIs and excipients, the particle morphology and particle size affect the consolidation characteristics and a positive relationship between the particle surface area and the mechanical strength of powders is generally accepted (Alderborn, 1996). Crystal structure, crystallinity and co-crystals may also change the compaction properties.

A tabletting process in control is the key to tablets having optimized technical properties and yet the compaction properties are not totally understood. Consequently, a greater understanding of the fundamentals of the consolidation characteristics of pharmaceutical materials is needed.

2.2 Objective and scope

The overall aim of this project was to quantify the compressibility and the compactibility of roller compacted granules, composed from different morphologic forms of calcium carbonate and different particle sizes of sorbitol and to describe the consolidation mechanisms.

The specific aims were:

- to improve the compaction properties of roller compacted granules. The effect of the process parameters of the roller compactor as well as the

effects of morphological forms of calcium carbonate and particle sizes of sorbitol were investigated (I).

- to investigate the granule fraction inhomogeneity of roller compacted granules from different morphologic forms of calcium carbonate and different particle sizes of sorbitol (II).

- to compare the compressibility and compactibility of granules from wet and dry processes, composed of different morphologic forms of calcium carbonate and different particle sizes of sorbitol (III).

- to investigate the mechanical stability over a 3 month period of tablets made from pharmaceutical sugar and sugar alcohols (IV).

The dissertation covers a review of the literature of compactibility and compressibility of powdery materials with emphasis on roller compacted granules in relation to results from own findings. The experimental work and a more thorough discussion of the results are presented in the papers and the manuscript which are enclosed as appendix I-IV.

3. Compressibility

Compression of tablets has been carried out as early as the 1900 century in a hand-operated device; this first really became an industrial success when the press became automated. Nowadays, the simplest applied pharmaceutical equipment for producing tablets is the single punch machine, the excentric press; mostly applied for research purpose and for preliminary evaluation of the tabletting properties in the development stage, as it only produces up to 4000

tablets/hour. The press compresses powdery material into a tablet in a die between a set of punches; thus a compressive force is applied from the upper punch only.

For industrial purpose, the more advanced and more productive multi-station tablet press, the rotary press are applied. The yield varies up to 500.000 tablets/hour depending on the number of punches and bulk properties of the material. In this press, compressive forces are applied from both upper and lower punches and from pre and main compression rolls. Newer models of rotary presses are computerized, instrumented with force transducers and the compressive force is hydraulic; all this combined, enables the preparation of tablets under controlled conditions.

For research purpose, compression is most often studied in a compaction simulator, capable of imitating the punch movement and speed of tablet presses with different pre and main compression forces. The compaction simulator consists of a single set of punches in a die, equipped with force and displacement transducers. Simultaneously to the measurement of the compression force, the powder height is measured as the displacement, which makes it possible to study the in-die compression behaviour. Measuring the out-of-die compression, it requires measuring the tablet heights of several tablets compressed at different compaction forces; however this is not only possible at a compaction simulator but also at tablet presses equipped with force transducers. The load is measured as the compression force and by dividing the compression force by the cross sectional area of the compact, the compression pressure is derived. The term pressure is more applicable than the force, since it enables the comparison of compression properties of different tablet sizes.

The compression cycle can be divided into the main sequences: Compression, decompression and ejection. During compression, the pressure increases to maximum while the punches are brought together. The punches part and the pressure decreases in the decompression phase. Finally, the lower punch ejects the tablet.

3.1 Compression mechanisms

Several authors have attempted to explain and describe the compression mechanisms. Two of the firsts were Cooper and Eaton (1962), describing the volume reduction of non-porous powders under a compressive force by this two-step explanation model: (i) Filling up large voids mainly by rearrangement of particles and to a lesser degree by local deformation: Fragmentation/destructive, elastic/recoverable and plastic/permanent. (ii) Filling up smaller voids by fragmentation and plastic deformation. Train and Lewis (1962) described the compression mechanisms as a particle rearrangement and local deformation almost similarly but with a third sequence to the mechanism: (iii) Elastic recovery may occur after ejection. Elastic recovery is material expansion which happens after the compression force is withdrawn from the compact.

The compression of granulated materials is a volume reduction of porous secondary particles composed of dense primary particles; thus adding more complexity into the mechanisms. Van der Zwan and Siskens (1982) proposed the following sequences in the compression of granules: (i) Filling of holes between the granules. (ii) Fragmentation and plastic deformation of the granules. (iii) Filling the holes between the primary particles. (iv) Fragmentation and plastic deformation of the primary particles. Recently, Johansson (1999) suggested a four step model for describing the compression of microcrystalline cellulose at increasing compaction pressure: (i) Repositioning of the aggregates at low

pressure. (ii) Local deformation, cracks and attrition of clusters of few particles. (iii) Bulk deformation and densification of aggregates. (iv) Volume reduction ceases. Both models do not consider the elasticity of the primary particles.

As it emerges from the proposed compression mechanisms of powders and granules, the predominately stages are: Rearrangement, fracturing, plastic and elastic deformation. Pharmaceutical materials normally consolidate by more than one of these mechanisms (Duberg and Nyström, 1985) and it most likely happens simultaneously (Wikberg and Alderborn, 1992). A great focus has been on estimating the elasticity, plasticity and brittle nature of pharmaceutical materials because the deformation characteristics are fundamental for the compaction. Plastic powders stay compressed when the compression force is removed whereas the elastic powders will to some extent return to the initial state after compression; sometimes resulting in capping and lamination of the tablet. Therefore, elastic behaviour of pharmaceutical substances is not wanted but to some degree expected as most particles undergo some elastic deformation. If the plastic deformation is dominating i.e. the interparticulate forces in a tablet are stronger than the elasticity of the material, the compact will remain compressed.

Brittle substances undergo particle size reduction during compression if a sufficiently large load is applied sufficiently fast enough to exceed a critical threshold (Rowe and Roberts, 1996). The degree of particle fragmentation during compression is of great importance, especially in direct compression where the effect on the compaction of adding dry binder (Mattsson and Nyström, 2000) and lubricant is less (De Boer et al., 1978). When the fragmentation occurs during compression new surfaces free of the binder or lubricant are created. These new surfaces are able to make bond formation to lesser and

greater extent in the absence of binder and lubricant, respectively (Duberg and Nyström, 1982).

In contrast to the pressure dependant fragmentation, the proportion of elastic and plastic deformation mainly depends on the applied pressure but also the duration of the loading (David and Augsburger, 1977). Therefore, the plastic/elastic deformation is often described as time-dependant, viscoelastic and viscoplastic because the behaviour of the material lies between elastic/plastic solids and viscous fluids (Müller, 1996). Consequently, a higher degree of plastic deformation can be obtained by slowing down the speed of tablet press if elasticity is a problem. Brittle substances, on the other hand, are less sensitive towards changes in the punch velocity.

3.2 Deformation characteristics

Applying a compressive force to a solid material will cause an axial dimensional change of the solid in a linear region as described by Hooke's law. The relative dimension change during compression, tension or indentation is the deformation strain (ε). The applied force normalized by the cross sectional area is the deformation stress (σ_d). In the linear region of the stress–strain correlation, the slope is denoted the Young's modulus (E) and quantifies the elastic deformation of a solid. For elastic deformation applies:

$$\sigma_d = \varepsilon \cdot E \qquad (1)$$

Exceeding a certain pressure limit, the deformation will change from elastic to plastic. This limit is termed the yield stress (σ_y) and quantifies the plasticity. Thus for plastic deformation:

$$\sigma_d = \sigma_y \qquad (2)$$

Fracture toughness determines the tendency of an interparticulate region to break during stress application and the following applies for brittle fracture (Rowe and Roberts, 1996):

$$\sigma_d = \frac{A \cdot K_{IC}}{\sqrt{D_p}} \qquad (3)$$

Where K_{IC} is the critical pressure intensity factor of the material, describing the stresses around an unstable crack or flaw and is an indication of the pressure required propagating a crack. *A* is a constant depending on the applied pressure, geometry of test specimen and crack and D_p is the particle diameter.

In the following, the most common methods are given for determining Young's modulus, yield stress, fracture toughness and other deformation characteristics of powder beds and compacts; thus single crystal techniques are disregarded.

3.3 Flexure testing

3.3.1 Estimating Young's modulus

Commonly, flexure testing also called beam bending has been applied for estimating Young's modulus (Kerridge and Newton, 1986; Roberts and Rowe, 1987, Mashadi and Newton, 1987a, Bassam et al, 1990). In bending techniques, a rectangular compressed powder specimen is subjected to transverse loads, resulting in dimension changes of the beam (Figure 1). The load is applied on two symmetrical places on one side of the massive beam and either on one or two symmetrical places on the other side; thus the testing can either be three- or four-point bending. Four-point beam bending is preferred due to the more uniform bending zone in the central section of the beam and due to no significant contribution of shear pressures (Bassam et al., 1990). However, three-point

bending has the advantage that it can be performed using low quantities of material (Roberts et al., 1989). In four-point beam bending, the applied load (F), the beam deflection (δ) and the beam dimensions (beam width: b, beam thickness: e, distances between the loads: a and l), the tensile stress (σ_t) and strain (ε) are calculated by (Bassam et al., 1990):

$$\sigma_t = \frac{3Fa}{e^2 b} \tag{4}$$

$$\varepsilon = \frac{\delta \cdot e}{2(\frac{l^2}{8} + \frac{al}{2} + \frac{a^2}{3})} \tag{5}$$

Accordingly, the stress-strain ratio from eq. (1) quantifies the Young's modulus at the particular porosity. Similar equation exists for three-point bending (Robert et al., 1991).

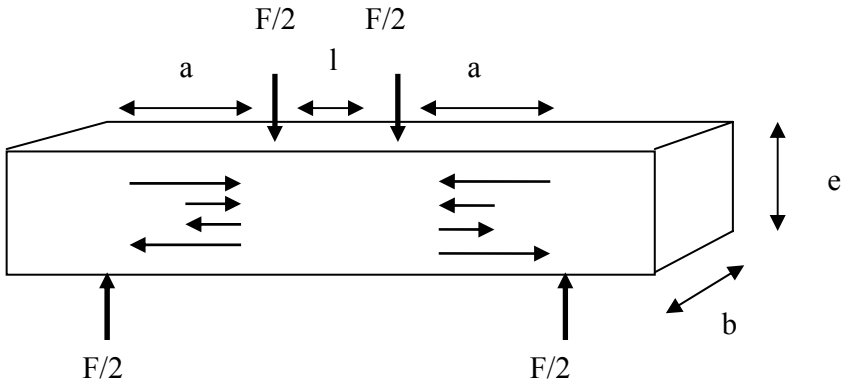

Figure 1: Four-point beam bending. The applied load: F and the beam dimensions (beam width: b, beam thickness: e, distances between the loads: a and l). ——►: Stress directions. ◄——►: Distance.

Generally, for larger pieces of solid materials, techniques for determining the Young's modulus and other deformation characteristics are less complicated than methods for compacted powders. Practical and theoretical limitations exist since the deformation characteristics depend on the ability to cohere and the porosity of the test specimen. The later problem has been handled by estimating the deformation characteristics at various porosities and extrapolating to zero porosity (Spriggs, 1961). Though approaching zero porosity, Young's modulus increases i.e. the elastic deformation decreases (Kerridge and Newton, 1986; Roberts and Rowe, 1987, Bassam et al., 1990). This phenomenon might be explained as particles in a dense beam are closely packed and therefore constricted in expanding. Similarly, increase in Young's modulus was observed for decreasing particle sizes (Bassam et al., 1990). Furthermore, specimen geometry and loading rate have been shown to affect the results (York et al., 1990), thus the result depends greatly on the method and a unique material constant of Young's modulus cannot be determined.

Bassam et al. (1990) ranked Young's modulus extrapolated to zero porosity for common pharmaceutical excipients, obtained in different beam bending studies. Generally, the following order was given: Starch < microcrystalline cellulose < sugars < inorganic fillers.

3.3.2 Estimating Poisson's ratio

By quantifying Young's modulus in flexure testing, only the longitudinal strain is considered. However, when applying a compressive force to the beam, the beam expands lateral at the two most separated loads and contracts at the centre load(s). In analogue to estimating Young's modulus, the shear modulus (G) is defined as the relationship between the radial deformation strain (ε) and the axial deformation stress (σ_d):

$$\sigma_d = \varepsilon \cdot G \quad (6)$$

The correlation between the axial and radial stress i.e. the correlation between the Young's modulus and the shear modulus, is the Poisson's ratio (ν) (Roberts et al., 1994):

$$\nu = \frac{E}{2G} - 1 \quad (7)$$

Especially in tabletting, the Poisson's ratio has been studied as in-die direct measurements of the axial and radial stress during compression. Summers et al. (1976) found Poisson's ratios for different crystal forms of common API's between 0.14-0.23. The variations between crystals forms within an API were between 0.04-0.07 mainly due to the crystal forms, but also due to granulation and different size fractions. In flexure testing, the Poisson's ratio for microcrystalline cellulose has been quantified to be 0.3 thus the shear modulus is 2-3 times smaller than the Young's modulus i.e. the longitudinal elasticity is larger than the lateral elastic deformation (Roberts et al., 1994)

3.3.3 Estimating the critical stress intensity factor (K_{IC})

Modifying the beam bending method by applying a crack in the beam, the critical stress intensity factor can be estimated as the single-edged notched beam (Rowe and Roberts, 1996). Similarly, in the radial edge cracked tablet method, a radial crack on the surface of a compact is introduced before the compact is compressed diametrically (Roberts and Rowe, 1989). The K_{IC} is estimated on basis of the crack size, beam/tablet dimensions and load (Kendall and Gregory, 1987; Mashadi and Newton, 1987ab; Roberts and Rowe, 1989) follows:

$$K_{IC} = \frac{F}{t}\left[\frac{c}{0.3557(d-c)^{3/2}} + \frac{2}{0.9665(d-c)^{1/2}}\right]\left[\frac{c}{2d}\right]^{-1/2} \qquad (8)$$

Where F is the peak load for cracking, c is the crack length, t is the tablet thickness and d is the tablet diameter.

Decreasing porosity and decreasing particle size increases the K_{IC} (York et al., 1990). The decrease in brittleness as the porosity decreases has been explained as a reduction in number and size of the pores, resulting in the source of defects is at a minimum when the beam is stressed (Mashadi and Newton, 1987b). Whereas for the particle size dependency; the probability of defects to exist in a crystal structure is reduced for smaller particles (Alderborn, 1996) and since the surface area is larger, smaller particles need a larger force in order to undergo fragmentation. The compression mechanism may also change from fragmentation to plastic deformation (Benbow, 1983), thus a material will reach a size limit where particles are too small to be size reduced further. Therefore, smaller particles often behave less brittle.

York et al. (1990) showed minor differences in brittleness of microcrystalline cellulose from different suppliers and different grades. It was concluded that the K_{IC} cannot be regarded as a unique material constant. Nevertheless, a general order of materials have been presented based on prior studies from different researchers (Rowe and Roberts, 1996): Non-steroidal anti-inflammatory drugs were very brittle (K_{IC}: 0.10-0.25 MPa·m^{½}), whereas sugars and sugar alcohols possessed intermediate brittleness (K_{IC}: 0.22-0.76 MPa·m^{½}) and the frequently studied microcrystalline cellulose had K_{IC} values between 0.76-1.42 MPa·m^{½}.

3.4 Indentation methods

The indentation hardness is defined as the resistance of a material to undergo local permanent deformation, when a hard object is pressed into the surface of the material and has mainly been applied for assessing the mechanical strength. However, the yield stress and Young's modulus can also be derived from this method. Thus, the yield stress is determined as one third of the indentation hardness (H) (Hiestand, 1985):

$$\sigma_y = \frac{H}{3} \tag{9}$$

Static and dynamic methods have been employed, though most utilized is the static methods: The square-based pyramid (Vickers indenter) has been applied for determining the Young's modulus and the critical stress intensity factor in crystals, while the spherical ball (Brinell indenter) has shown to be more suitable for compressed tablets. In the static tests, the indenter is pressed into a material for a short period and if the material is brittle or plastic the indentation will appear after removal of the load. However, if the material possesses elasticity, the material will expand and reduces the dept of the indentation. The elastic recovery (Δh) is determined as the difference in the penetration dept under load (h_1) and after removing the load (h_2). From this, the Young's modulus has been estimated as (Ridgway et al., 1970):

$$E = 0.268 \cdot \frac{L_2}{\Delta h \sqrt{h_1}} \tag{10}$$

Where the L_2 is the load required to push the load the sphere back into the indentation.

In the dynamic tests, a pendulum has been dropped down on a compact and the rebound height was applied for estimation the hardness (Hiestand et al., 1971).

Characteristic for the indentation methods; the results depends on the tablet manufacturing process as well as the indentation method (Jetzer et al., 1985). Factors as tablet press principle, dwell time during compression and testing period may affect the result, thus limiting the comparison of the results from these methods.

3.5 Specific surface area and pore structure

An approach to quantify the degree of fragmentation indirectly is to measure the surface area of a powder before compaction and measure the compact at increasing compaction pressures by permeability (Alderborn and Nyström, 1985) or gas absorption techniques (Duberg and Nyström, 1982). Results from a Blaine gas permeability apparatus, where the specific surface area of a powder is derived from the resistance of a gas to flow through a powder bed, showed significant increases in the surface area of fragmentation materials (Alderborn and Nyström, 1985). Information about pore size distribution in a tablet can be obtained by mercury penetration in a various range of penetration pressures (Orr, 1969/1970). Thus, compression of granules, manufactured from a highly brittle material, the intergranular pores are reduced in size and the pore size distribution changed (Wikberg and Alderborn, 1993). In dry granules of lactose, a finer pores size distribution and a larger specific surface area were detected in tablets made from a fine fraction of granules (63-106 μm) than coarse granules (212-425 μm) (Riepma et al., 1993).

3.6 Visual inspection

The inspection of tablets by scanning electron microscopy (SEM) enables studying of the physical properties during compaction. Changes in particle size due to fragmentation and change in particle shape as a result of plastic deformation was reported by De Boer et al., (1978) in a study of compression behaviours of excipients with and without lubricant. From this method, small cracks and pores can also be detected. Duberg and Nyström (1982) concluded that studying the SEM pictures is a useful method for obtaining a qualitative measure of the fragmentation. However, this method depends very much on the user and his ability to be objective. Further, the size of the sample is very small and may not represent the whole tablet.

3.7 Pressure profiles

Many authors have attempted to describe the compression process mathematically in order to obtain more knowledge about the volume reduction / densification of a powder bed under pressure. Some mathematical models are oversimplified and do not fit the data satisfactory while other equations have been derived due to the curve-fitting capability of the equations rather than considerations about the underlying physical properties (Bockstiegel, 1966). An example of this is the Kawakita equation having two constants characterising the powder compressing; though with doubtful physical meaning (Paronen and Ilkka, 1996). In order to keep the models accessible, the equations express the compression data in a simple linear relationship after transformation. During the recent decade, the spreadsheet programs have improved greatly, making it possible to apply non-linear regression exploring the data (Sonnergaard, 2001). The advance of these non-linear models is to describe the complexity of the data with a better fit. Older models are still applied; the Heckel equation has been

very popular while the Walker model has obtained less attention despite it possesses a better curve fitting ability (Sonnergaard, 1999).

3.7.1 Heckel equation

The most well-known compression equation (eq. 11) was introduced by Heckel in 1961 for describing the plastic densification of metal powders during compression (Heckel, 1961a):

$$\ln\left(\frac{1}{1-\rho}\right) = KP + A \qquad (11)$$

Where ρ is the relative density of the material, K and A are constants and P is the compaction pressure. Thus the Heckel equation is based on the assumption that the change in density due to applied pressure is directly proportional with the remaining porosity. Plotting the ln(1/(1-ρ)) as a function of the compaction pressure, a straight line relationship exists in the pressure range around 50-200 MPa (Rowe and Roberts, 1996). Due to a poor fit of the model, the constant A is only obtained from the intercept of this extrapolated slope and not from the modelled values. The slope, K was suggested to quantify the plastic deformation of the metal powders, since these materials were not expected to possess any elasticity or fragmentation (Heckel, 1961b). The K value was related to the yield strength (Y) of the material by a factor 3:

$$K \approx \frac{1}{3}Y \qquad (12)$$

The yield pressure is defined as the stress at which a material begins to deform plastically. In 1971, Hersey and Rees defined the reciprocal of the slope as the yield pressure in a study of determining whether the predomination compression mechanism was fragmentation or plastic deformation. Linear plots were obtained

from materials deforming plastically, while curved plots came from brittle substances. Due to the curved form of the plots, the linear region is difficult to determine and consequently the result is affected (Robert and Rowe, 1985).

Generally in out-of-die measurements, the reciprocal of the slope is called the mean yield pressure and for in-die measurements, it is named the apparent yield pressure. Similar results for in-die and out-of-die measurements were originally obtained for Heckel (1961a) testing metal powders. However, for materials exhibiting a high degree of elasticity and therefore a large strain recovery after pressure removal, the in-die and out-of-die measurements have shown to deviate much (York, 1979, Paronen and Juslin, 1983, Paronen, 1986).

Several authors have suggested subdivision of the Heckel plot for obtaining more information of the porosity-pressure function. Some of them, Duberg and Nyström (1985) divided the plot into three phases. In phase I, initially when the applied pressure is relative low, the porosity reduction was related to fragmentation behaviour of the materials. Phase II – the linear slope was shown to reflect the total deformation ability and not only the plastic deformation as suggested by Heckel. Whereas the phase III the decompression phase, elastic deformation was evaluated as percentile increase in porosity.

Nowadays, the mean yield pressure and the apparent yield pressure are applied widely for determining the compressibility of pharmaceutical powders. However, the equation is much criticized (Pedersen and Kristensen, 1994; Rue and Rees, 1978, Sonnergaard, 1999). One of the major concerns is the yield pressure depends greatly on the experimental setup. York (1979) compared published resulted of microcrystalline cellulose from earlier studied and found a mean yield pressure varying from 158 MN/m^2 to 218 MN/m^2 – a difference of 28 %. The large variation was mainly ascribed to the dimension of die and

punches (York, 1979). Other research results showed that the apparent mean yield pressure was confounding with the pycnometric density (Humbert-Droz et al., 1983). In addition, differences in the mean pressure due to the experimental setup include the sensitivity towards lubrication. De Boer et al. (1978) found the effect of lubrication to be more pronounced in plastic deformable materials than brittle materials. Likewise, increasing punch velocity enhanced the yield pressure for ductile materials whereas the brittle materials very unaffected (Roberts and Rowe, 1985). Thus a strain rate sensitivity index was suggested as a percentage increase in the yield pressure from low to high punch speed (Roberts and Rowe, 1987).

The lack of reproducibility among different studies may also depend on differences in the solid state properties of the materials, thus particle size and differences in the manufacturing of the powdery materials were connected to the yield pressure (Fell and Newton, 1971; Roberts and Rowe, 1986). In spite of all the large variations in the yield pressure, the method also failed to discriminate between very different substances as microcrystalline cellulose and sorbitol (Sonnergaard, 2000). However, regardless of excessive critical evaluations of the Heckel plot, it still remains the most popular quantification of the compressibility.

3.7.2 Walker equation

The Walker equation was one of the first mathematical models to fit compaction data (Walker, 1923). It describes the change in specific volume (SV) of a powder bed when pressure is applied (P), where the specific volume is the tablet volume, normalized by the tablet mass. The Walker coefficient, W is the absolute value of the slope of the Walker plot (Walker, 1923):

$$SV = -W \cdot \log(P) + A \qquad (13)$$

Where A is a constant.

The Walker equation was introduced to the pharmaceutical research area by Train (1956) who investigated different stages of compression of magnesium carbonate. Sonnergaard (1999) concluded that the Walker plot was superior to the Heckel plot in fitting in-die compression data of pharmaceutical powders and in discriminating between the materials. In addition, Patel et al. (2007) reported a better discrimination power of the Walker plot than the Heckel model in a compression study of different size fractions of paracetamol. This was related to the influence of the elastic deformation and the applied pressure on the Heckel parameter. From the Walker coefficient, increasing compressibility was obtained by decreasing paracetamol size fractions. In a study of different morphological forms of calcium carbonate powder, the scalenohedral structure of calcium carbonate obtained a larger Walker coefficient than the cubic and the irregular calcium carbonate (I). This difference was explained as the large initial volume of the scalenohedral calcium carbonate. The addition of sorbitol improved the Walker coefficient for all the calcium carbonates. Especially the smallest sorbitol, having a particle size of 45 μm, had an enhancing effect of the Walker coefficient (I). Similar differences in the Walker coefficient were observed for decreasing particle sizes of sodium chloride, sucrose and quartz (Huffine and Bonilla, 1962).

3.8 Force-displacement profiles

Alternative to correlating the compression behaviour with the compression pressure, the compression behaviours have been related to the energy input or the work of compression derived from force-displacement curves by integration

(Antikainen and Yliruusi, 2003; De Blaey and Polderman J., 1970; Oates and Mitchell, 1989). Small insignificant amounts of energy are needed for particle rearrangement and for interparticulate friction; but due to the minor occurrence and practical limitations in performing the estimation, it is normally not determined. Large amounts of energy are consumed by friction between particles and die wall whereas some of the elastic deformation is recovered during expansion. Thus when calculating the work of compression, the overall work applied to compress a tablet should be subtracted the work of die wall friction and the work recovered during decompression.

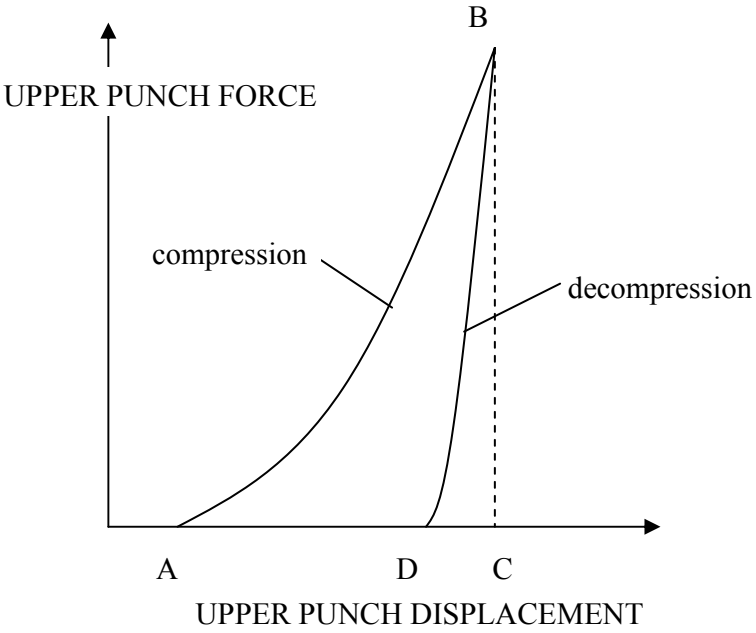

Figure 2: The upper punch force versus the upper punch displacement; showing the compression and decompression curves.

In figure 2 the area ABC represents the total work consummation during compression. Thus the work of compression can been obtained from measurements of upper punch force and upper punch displacement as the total area under the curve of upper punch force versus upper punch displacement (ABC) and substracting the die wall friction and the work of expansion (BCD). The die wall friction has been determined as the difference between the work of compression of unlubricated granules and lubricated granules, assuming no significant die wall friction is present in compression of lubricated materials (Nelson et al., 1955). De Blaery and Polderman (1970) calculated the energy needed to overcome the die wall friction as the work of compression for upper punch forces minus the work of compression for the lower punch force because the lower punch is assumed to be independent of the die wall friction.

For determining the elastic recovery during decompression, the area BCD can be estimated. However, as De Blaery and Polderman (1970) pointed out, the recovered energy during decompression does not account for the energy recovery after removal of the upper punch. Instead, a double compression was performed and the energy needed for the recompression was defined as the work of expansion.

The shape of a force-displacement profile will depend on which deformation mechanisms are dominating. Plastic or brittle materials give a large work of compression (ABD) whereas the work needed to compress elastic materials is recovered during decompression and consequently the area ABD would disappear for an ideal elastic material. Since the absolute size of the area depends on the compression forces, the ratios of the areas have been more applicable when quantifying the compressibility or the elastic deformation. The distance DC divided by the distance AC has been applied as a measurement of elastic deformation (Antikainen and Yliruusi, 2003). Likewise, Young’s

modulus was calculated from the ratio between the work of decompression and the work of compression for tablets compressed at several compression forces (Dwivedi et al. 1991). However, since the compression was performed on a rotary tablet press, the punch displacement was technical difficult to measure thus the tabletting cycle time was determined instead of punch displacement (Dwivedi et al. 1991). The difference between the maximum compression pressure and the compression pressure at the maximum displacement has been utilized as quantification of the plastic deformation (Antikainen & Yliruusi, 2003), assuming the plastic deformation is time-dependant and fragmentation depends only on the compressing pressure (David & Augsburger, 1977).

4. Compactibility

4.1 Compaction mechanisms

The characterisation of powder compaction plays an important role in the manufacturing of tablets. Nevertheless, it's still unknown why some powders cohere into a compact while other powders are unable to form mechanical a resistant tablet.

During volume reduction, the particles in the powder bed are brought together in close contact by a compressive force; enabling the interparticulate attraction forces on the particle surface to act. As a result, bonds may be formed, converting the powder into a compact. The ability of a powder bed to form a coherent tablet depends on the dominating bond mechanism and the bonding surface area. Since the bonding mechanism and bonding surface area are difficult to determine, secondary factors as particle shape, particle size and bulk properties have often been studied. The interparticulate bonding mechanisms

have been classified by Rumpf (1958) and the ones relevant for compaction include the following types:

- Attractions between solid particles

- Solid bridges

- Shape-related bonding (Mechanical interlocking)

- Non-freely-movable binder bridges

The three first are the most important during compaction, but as a result of air humidity, the last mechanism cannot be disregarded (Nyström and Karehill, 1996). In addition, it is clear that several mechanisms can be active simultaneously during compaction (Karehill and Nyström, 1990).

4.1.1 Attraction between solid particles

The attraction forces between solid particles include van der Waals forces and electrostatic forces (Führer, 1996). Due to the predominant ductile nature of pharmaceutical materials, Van der Waals forces are expected to be the dominant bonding in compaction of tablets (Nyström and Karehill, 1996), thus the forces are acting as minor charges or polarization of atoms of the molecule (Führer, 1996). The forces require a short interatomic distance and a steric arrangement. The electrostatic forces, on the other hand, are interactions of highly charged particles, being active over a relative long distance. The charges are distributed on the particle surfaces either uniformly as on an amorphous spherical particle or heterogeneously as on a milled irregular particle with higher charges on the edges (Führer, 1996). Many pharmaceutical crystalline materials have a polar surface. The electrostatic forces include hydrogen bonds, which are of particular

importance in direct compression of microcrystalline cellulose, starch and lactose.

4.1.2 Solid bridges

The solid bridges form strong bonds of particles, fusing together through partial melting at high pressures at the point of contact. At the bond formation the primary particles loses their individually characteristic and even a separation of the primary particles will not result in the original particles (Führer, 1996).

4.1.3 Mechanical interlocking

Mechanical interlocking is depending on the particle shape. Needle-formed and irregular particles are more likely to hook and twist during compacting than spherical particles. Furthermore, bulky materials are also expected to bond by interlocking.

4.1.4 Non-freely-movable binder bridges

The non-freely-movable binder bridges are ad- and cohesion forces caused by a thin liquid layer. This mechanism is active in slightly moist fine particles since the distance between the particles decreases and consequently increases the interparticulate contact area. When the non-freely-movable binder bridges are present, the interparticulate forces of van der Waals and electrostatic forces are depressed (Karehill and Nyström, 1990). Consequently, moist and temperature can chance the powder compaction properties.

4.2 Measuring the mechanical strength

The ability of a powder bed to form a mechanical resistant tablet is most often tested by the resistance towards a destructive force. The result greatly depends

on the testing method; as the pressure direction can be either radial or axial and the type of pressure can be tensile or compressive strength. Some of the most common are presented in the following.

The environmental related parameters also affect the mechanical resistance of tablets. The time and storage condition between compression and testing also are significant (IV). Therefore, to set a standard, most compaction studies include 24 hours storage and a thorough description of the storage conditions are normally given.

4.3 Diametral compression

In the 1930'ies, the diametral compression test was developed for measuring the mechanical strength of tablets in a crushing force tester. Nowadays, the resistance to crushing of tablets is a standard test described in Ph. Eur (European Pharmacopoeia, 2.9.8., 2007) and it is applied for in-process control and end product control inspection in pharmaceutical manufacturing. The popularity of the compression test lies in the ease of conduction as well as the high performance of the crushing force testers, thus a high reproducibility between 16 testers and high repeatability within most of these testers have been reported (Sonnergaard et al., 2005). However, the loading rate has been claimed to have significant impact on the measured crushing strength (Rees et al., 1970; Newton et al., 1986). In a study of tablets, compressed at loading rates corresponding to jaws speeds between 0.05-5 cm/min, it was concluded that increasing loading rates resulted in increasing crushing forces (Rees et al., 1970). This range was though exceeding the normal working area of commercial crushing force testers. Therefore, Sonnergaard et al. (2005) tested the variation in crushing force for microcrystalline cellulose and lactose tablets compressed in a normal range:

0.25-5 mm/s and found no effect of loading rate. Consequently, the diametral compression test appears to be robust compared to other quality parameters.

4.3.1 Radial tensile strength

The use of the diametral compression test for estimating the radial tensile strength, also called the Brazilian test, was originally devised for measuring concrete (Carneiro and Barcellos, 1953). Later, Fell and Newton (1968) introduced the indirectly estimation of the tensile strength of tablets to the pharmaceutical research field. The radial crushing strength of a tablet is determined as the force needed to crush the tablet applied radically by one of two opposite facing jaws. Commonly in pharmaceutical science, the tensile strength is calculated from the crushing force (F) as it is independent of tablet dimensions. The calculation is based on elastic deformation theory, thus the application of a compressive pressure will contract the tablet longitudinal in the line of loading while the tablet will expand lateral until tension failure happens. However, only the fracturing of tablets through the line of loading are considered as tension failure and only these tablets are applicable for determining the tensile strength (Fell and Newton, 1970). The tensile strength (TS) is defined as (Fell and Newton, 1970):

$$TS = \frac{2F}{\pi Dh} \tag{14}$$

Where D is the tablet diameter and h is the tablet thickness of a flat-faced cylindrical tablet.

The validity of the indirectly tensile strength measurement has been questioned as it is uncertain whether the test actually causes failure in tension (Darvell, 1990). The theoretical basis of calculating the tensile strength relies on the

assumption that the test material is homogenous, isotropic and elastic. However, it is well-known that tablets are heterogeneous, the stress distribution in tablets is anisotropic and pharmaceutical materials only deform elastically to a minor degree. As a result, the crack rarely initiate at the center and propagates outward (Hondros, 1959), which it expected for an ideal elastic and isotropic material. Further, miscalculation can possibly occur from the line of loading. As Fell and Newton (1970) pointed out themselves; an ideal line of loading will never occur because the load will be distributed over an actual contact area due to flattening of the tablet, thus preventing line loading as well as reducing shear and compressive stresses. Nevertheless, the indirect tensile strength will remain the most well-known determination of the crushing strength.

4.3.2 Specific crushing strength

A method to estimate the mechanical strength from the diametral compression test and independently of the tablet dimensions is the specific crushing strength (*SCS*) (Spengler and Kaelin, 1945; De Jong, 1991; Sonnergaard, 2006). For a flat-faced cylindrical tablet, the specific crushing strength is defined as the crushing force (F) normalized by the cross-sectional area ($D \cdot h$):

$$SCS = \frac{F}{Dh} \tag{15}$$

This term resembles other widely applied methods for determining the tensile strength, where the breaking force is corrected with the cross-sectional area in compression and tensile testing (Nyström et al., 1978; Jarosz and Parrott, 1982; Newton et al., 1992). The specific crushing strength deviates mathematically from the indirectly measured tensile strength (eq. 14) only by the factor $2/\pi$ and therefore it has the same power in discriminative analysis (Sonnergaard, 2006).

However, the specific crushing strength is simpler and leaves out erroneous assumptions.

4.3.3 Axial tensile strength

A direct approach for determining the axial tensile strength was developed (Nyström et al., 1977), where tablets were fixed with cyanoacrylate adhesive to a pair of adapters and pulled apart in a tensionmeter. The axial tensile strength (TS_{ax}) was calculated as the maximum tensile force normalized by the cross-sectional area ($4/(D^2 \cdot \pi)$) (Nyström et al., 1978):

$$TS_{ax} = \frac{4F}{\pi D^2} \tag{16}$$

In a comparison of the direct axial tensile strength (eq. 16) and the indirect radial tensile strength (eq. 14), a decreasing axial tensile strength at high compression forces of tablets compressed at an excenter tablet press was associated with capping tendency on a rotary tablet press (Nyström et al., 1978). The radial tensile strength, on the other hand, increased as the compaction force was increased and therefore did not indicate the capping tendency. Later, this method was tested with different excipients and the result was confirmed for tablets of granules expected to form caps (Jarosz and Parrott, 1982). Consequently, evaluating the direct axial tensile strength is a useful tool in predicting capping tendencies of a tablet formulation at a single punch tablet press, thus capping normally does not reveal before upscaling to a rotary tablet press.

The tensile strength of cubic compacts was evaluated in a tensiometer as the direct axial and radial tensile strength and compared with the indirect axial and radial tensile strength, determined by compression (Newton et al., 1992). Similarly for all the tests, the tensile strength was calculated as the breaking

force divided by the cross-sectional area. It was noted that the direct method represented the minimum tensile strength because the tensile test broke the compact in the weakest plane while the compact was fractured in a fixed line of loading in the compression test.

4.3.4 Work of failure

The mechanical strength can be expressed as the work of failure which is the total work needed to crush a tablet, calculated by numerical integration of the applied force with respect to the displacement of the moving jaw in the compression tester. This method is technical more complicated than determining the radial crushing strength; however studying the stress-strain curves delivers a better characterisation of the materials, including the effect of the material's ability to deform during the tablet failure. Thus a tablet crushed at a high force and low strain possibly will be more prone to breaking during handling than a tablet of high strain at a lower maximum crushing force (Schubert et at., 1975). This difference is seen for the deformation characteristics; thus ductile tablets generally require a high work of failure due to a high crushing strength but also due to the considerable deformation during crushing whereas brittle tablets deform less in the compression tester (Rees and Rue, 1978). Therefore, Rees and Rue (1978) concluded that work of failure is a better and more informative quantitative assessment of mechanical tablet properties than tensile strength.

4.4 Flexure testing

The beam bending applied for determining the deformation characteristics was originally developed for estimating the mechanical strength from load fracture (Münzel and Kägi, 1957). The tensile strength for four-point beam bending is determined as the tensile stress at fracture by eq. 4. For determining the tensile

strength from tablets, three-point bending of tablets has been applied (Endicott et al., 1961; Amin and Fell, 2002) and is calculated as:

$$TS = \frac{3L_{br}c}{2De^2} \qquad (17)$$

Where L_{br} is the breaking load, c is the distance between the supports, D is the diameter and e is the tablet thickness. The stress distribution in the beam during bending is non-uniform as it varies from zero at the central axis to maximum at the outer surface (Figure 1). The stress distribution at the surface has a large impact on the measured strength and therefore result from this test is considerably higher than results from indentation hardness and diametral comprssion tests (Berenbaum and Brodie, 1959). Results from the three-point beam bending of tablets were significant larger than results from the diametral compression test (Amin and Fell, 2002), which was explained as the marked tablet inhomogeniety, thus the density was considerably higher at the surface than the inner material. Nowadays in pharmaceutical research, this method is not in focus due to its relative high complexity and due to the questioning of the results.

4.5 Indentation hardness

Expressing the mechanical strength of a material independent of the tablet geometry is possible as indentation hardness (H) also called the Brinell hardness number (H_b). A spherical ball is pressed into a compact and the resistance of the material to undergo local permanent deformation is defined as the indentation hardness, quantified as the applied force (F_i) divided by the projected area of indentation (Rowe and Roberts, 1996):

$$H = \frac{F_i}{\pi D_i h_1} \tag{18}$$

Where D_i is the diameter of the indenter ball and h_1 is the maximum indentation dept during indentation. Before it was possible to measure the indentation dept precisely, the projected area of indentation was calculated from the diameter (d) of the impression, measured from SEM micrographs (Jetzer et al., 1983). Thus the indentation hardness has been calculated from (Ridgway et al. 1970; Leuenberger, 1982):

$$H = \frac{2F}{\pi D(D - \sqrt{D^2 - d^2})} \tag{19}$$

Eq. 19 presumes that the elastic recovery is negligible, thus the removal of the load leaves an indentation that does not change in diameter.

The indentation hardness is preferred over the diametral compression test when the material has capping tendencies because the crushing strength measurement will not be valid. However, this method holds some limitation since the indentation hardness depends on the measuring position on the tablet. In a study of the surface hardness of tablets, generally larger values were obtained from the tablet surface adjacent to the moving punch and a decrease in hardness was reported from the centre of the tablet to the outer edge (Ridgway et al., 1970). On the other hand, the indentation hardness has also shown to be a suitable method for estimating the mechanical strength of ribbons, the compressed compacts from the roller compactor (Freitag et al., 2004).

4.6 Pressure profiles

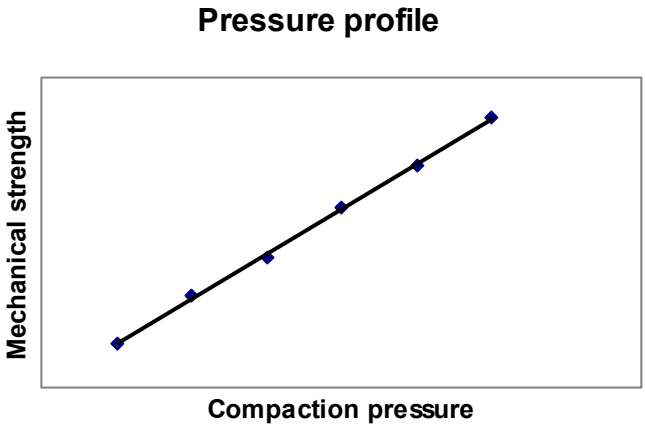

Figure 3: Pressure profile: The mechanical strength as a function of the compaction pressure.

The mechanical strength is often reported as a single-point measurement at a given compaction pressure. This set-up avoids any assumptions about a mathematical relationship between mechanical strength and compaction pressure (Sonnergaard, 2006). However, at this rather limited information level, it is not possible to compare tablets, compacted at different compaction pressures. Therefore, the mechanical strength should be characterized and quantified as the compactibility; the mechanical strength as function of applied compaction pressure (Figure 3) (I).

The compaction profile shows a sigmoid shape (Rees and Rue, 1978; Sonnergaard, 2006). Just above the lower pressure threshold the mechanical strength increases slowly and then more rapidly in the linear region until the upper pressure limit is reached, where the mechanical strength levels off or even decreases due to capping or lamination (Alderborn, 2003). At low pressures, the

increase in mechanical strength has been described by a power function with increasing compaction pressure (Kuentz and Leuenberger, 2000):

$$TS = kP_{\max}{}^{T/2} \qquad (20)$$

Where *TS* is the tensile strength, *k* and *T* is constants and P_{max} is the maximum compaction pressure. The linear region of the compaction profile covers the relevant compaction pressures for tablet formation. A linear model for the tensile strength of lactose monohydrate was described for tablet masses of 0.4 -1.0 g in a range up to 310 MPa (Newton et al., 1971), causing a general model to be proposed based on the tensile strength (Newton et al., 1972). Expressing this model as the specific crushing strength (*SCS*) has also been applied thus (Sonnergaard, 2006, I and III):

$$\mathrm{SCS} = \mathrm{C_P} \cdot \mathrm{P} + \mathrm{A} \qquad (21)$$

Where C_P is the slope, applied for quantifying the compactibility and *A* is the intercept. A higher correlation coefficient between tensile strength and compaction pressure was obtained by a linear model of the double logarithmic function (Newton and Grant, 1974) because the large deviations at the higher values become relative smaller by the logarithmic functions. However, this model has no scientifically basis and the slightly increase in the correlation has no practical significance.

Based on a Weibull distribution, a pressure profile was suggested (Castillo and Villafuerte, 1995):

$$\ln(-\ln(1 - TS / TS_{\max})) = n \cdot \ln P + B \qquad (22)$$

Where *TS* is the tensile strength; TS_{max} is the maximal tensile strength; *n* is the slope, applied for quantifying the compactibility and B is the intercept. This model fitted data at compaction pressures (*P*) ranging up to 980 MPa, exiting the relevant compaction area greatly.

4.7 Friability

The friability test is the most direct method to assess how well tablets are going to stay intact during handling; as it is a measurement of the remaining tablet weight of tablets that have been rotated in a drum, leaving out the dust and cracked tablets. The test is a Ph. Eur requirement for uncoated tablets and a maximum lost of 1.0 % is acceptable (European Pharmacopoeia, 2.9.7., 2007). In an evaluation of tablet dimensions, the largest mechanical wearing away was obtained from tablets with sharp edges and a large diameter whereas the tablet thickness did not seem to affect the friability (Spengler and Kaelin, 1945). The friability of tablets is generally decreased by the addition of a binder as the tablets deform more plastic. In a study of different qualities of magnesium carbonate and different types of powdered cellulose, roller compaction mostly reduced the tablet friability in comparison to direct compression of the materials (Freitag et al. 2005).

4.8 Process analytical technology (PAT)

Recently, the process analytical technology has been applied for predicting the mechanical strength of tablets. PAT has been a valuable tool in the pharmaceutical industry to obtain process understanding thus the analytical tools have been applied for monitoring powder blend homogeneity and moisture content as well as testing the content of uniformity in tablets. PAT covers the use of spectroscopic techniques combined with multivariate statistics, the chemometrics for handling the large data material. Rapid, non-destructive near-

infrared spectroscopy (NIR) has mainly been applied for predicting the mechanical strength. Setting up a method is necessary in order to interpret the spectra. Therefore, a multivariate calibration is applied for generating an equation based on the correlation of series of absorbance bands to varying crushing forces, obtained normally from the diametral compression test. Results from NIR hardness prediction have been shown to be as least as precise as the diametral compression test (Morisseau and Rhodes, 1997). Further, the NIR hardness prediction was shown to be robust over a 1-20% range of drug potency (Kirsch and Drennen, 1999).However, NIR and raman were also applicable in predicting the tablet porosity (Tawakkul et al., 2006). Therefore, there is a potential risk that the NIR is predicting the porosity in stead of the mechanical strength, thus batch-to-batch variations may influence the mechanical strength and perhaps not the porosity, resulting in erroneous process monitoring.

4.9 Relationship between compactibility and compressibility

A compressibility parameter has been derived from the mechanical strength of tablets in few investigations (Leuenberger, 1982; Alderborn, 2003) whereas other researchers have performed an actual comparison of compressibility and mechanical strength. Çelik and Marshall (1989) presented data of common pharmaceutical excipients, where the total work of compression correlated with the tensile strength. Previously, the compressibility expressed as the apparent mean yield pressure obtained from the Heckel plot failed to correlate with the tensile strength of roller compacted magnesium carbonate (Freitag and Kleinebudde, 2003). However, a correlation between the tensile strength and the degree of densification was possible; the densification was expressed as the ratio between the relative density of the tablet and the relative density of the bulk material. Recently, a linear relationship between the Walker coefficient and a compaction parameter derived from the pressure profile (eq. 21) based on the

specific crushing strength (eq. 15) was demonstrated for a wide range of pharmaceutical powders (Sonnergaard, 2006). Following, this relationship was also illustrated for roller compacted and wet processed granules of different combinations of calcium carbonate shapes and sorbitol sizes (I and III).

5. Roller compaction

One of the first patents in roller compaction was given for the manufacturing of fuel briquettes from coal waste in the middle of the nineteen century. The briquettes were compressed directly through two counter rotating rolls with deep pockets in the roll surface. Following the manufacturing of metal sheets and flakes was developed. Parallel at the pharmacies a dry granulation method; slugging was developed for improving die-filling in a tablet press of poor flowing powders. The powder was compressed into soft tablets and ground, resulting in the formation of mixture of coarse granules and many fines. Early roller compactors were developed in the 1950'ies for the pharmaceutical industry. Nowadays, the requirement for cheap large scale processes has re-established the interest for roller compaction.

5.1 Agglomeration method

Producing roller compacted granules, the powder enters the roller compactor in the hopper and is conveyed by a screw to the rolls (Figure 4). Arriving at rolls, the densified powder is compressed between to counter rotating rolls under pressure, forming a dense ribbon. Finally, the ribbon is milled into granules through a sieve.

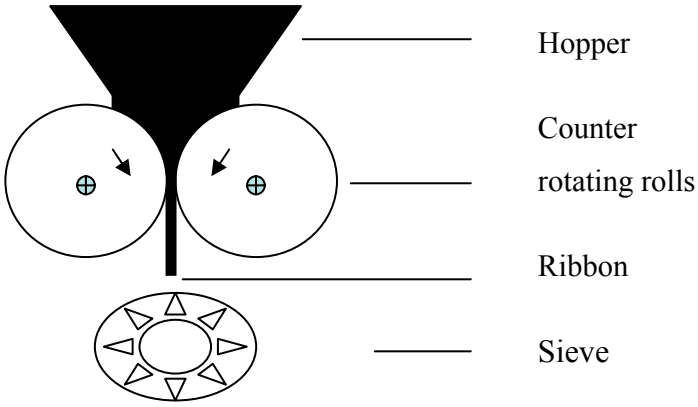

Figure 3: Schematic drawing of the roller compactor, having a funnel in the top, two counter rotating rolls, forming a ribbon and a sieve in the bottom.

The roller compactors of different sizes and manufacturers consist of the same elements but the machine design varies which may yield different results. The configuration of the machines and the differences will be pointed out in the following. Starting at the top, the hopper design may be conical or box-shaped though without major importance. Moving down, the feeding system is essential for delivering a uniform and continuous material flow, needed in order to compress a homogeneous and dense ribbon (Guigon and Simon, 2003). The gravity is the simplest system which requires a free-flowing powder with a large bulk density. However, for pharmaceutical application the feeding is normally a force-feeding screw which helps deaerate the fine powder and thus facilitates a more dense ribbon. Often two screws are used as feed and tamp augers: The feed auger is controlling the amount of material delivered to the feeding zone whereas the tamp auger is enhancing the densification before compression. The two screws can either be horizontal and vertical or visa versa depending on the configuration of the rolls. The rolls can be mounted

horizontal and subsequently the feed auger must be vertical. In other cases the rolls are vertical or inclined position as the Gerteis at 30 degrees. Newer machines have a movable roll which makes it possible to adjust the gap automatic in order to keep the compaction pressure fairly constant if the throughput is varied (Simon and Guigon, 2003). This is advantageous in order to keep the density and mechanical strength of the ribbon constant and thereby reduce the amount of fines. The process parameters are covariating, thus the alteration of auger speed, roll pressure or gap will change one of the other parameters. As an example, increasing the feed and tamp auger speeds will increase the roll pressure at constant gap, resulting in a denser ribbon.

As the machines come in lab -, pilot - and production sizes the roll diameters are different; though some fabricants keep the roll diameter constant in their machines to ease the scale up. A larger roll diameter favours a long compression zone i.e. a higher dwell time. The rolls are mounted on frames which can be a cantilever shaft or a mill-shaft frame. In the cantilever shaft the rolls are located outside the frame and hold the rolls from one side. The mill-shaft frame bears the rolls from both sides making this design more stable and less prone for unparallel rolls. A hydraulic system is used to exert pressure on the frames. The pressure readings are not comparable among different machines designs since the pressures measurements rely on different measuring principles and the units are different.

The roll surface can be smooth, knurled or deep pockets. The smooth surface is mostly used for calibration or for sticky materials because they fail to convey the powder due to low friction. More rough rolls drag the material into the compaction zone with greater force than the smooth rolls (Johanson, 1965). Consequently, the knurled rolls have shown to be applicable for pharmaceutical purpose, thus knurled rolls have a small pattern giving only a small variation in

density of the ribbon; unlike the pocket rolls which are mostly used for producing briquettes. Small variation in density of the ribbon is advantageous since it involves a smaller amount of fines.

Funakoshi et al. (1997) introduced the fitting of the rolls as a concavo-convex roller pair as leakage is reduced to a minimum and an even ribbon density can be obtained. Furthermore, Funakoshi et al. (1997) found the optimal angles of the wall slopes to be 65° in order to avoid adherence to the rolls. Nowadays, similar roll configurations are implemented in all new machines.

5.2 Agglomeration mechanisms

The principle of the roller compaction was described by Johanson (1984) as three zones in which the material passes through. Following Guigon and Simon (2003) used new and more descriptive terms: The feeding zone, the compaction zone and the extrusion zone (Figure 5). The powder is entering the feeding zone where the densification only happens to a small extent as a result of the rearrangement of the powder. The transition to the next zone is defined by the nip angle, which depends on the roll geometry and the powder packing properties; thus large rolls and highly compressible materials enlarge the nip angle. The frictional forces, caused by the surface of the rotating rolls, are conveying the powder into the compaction zone where the densification of powder is done by the roller pressure. When the powders reach the gap which is the narrowest distance between the rolls, the powders are deformed plastic/elastic or/and the material is fragmented. After passing the gap the material leaves through the extrusion zone forming a dense ribbon which often will expand elastic. Following, the ribbon is milled into granules through a sieve.

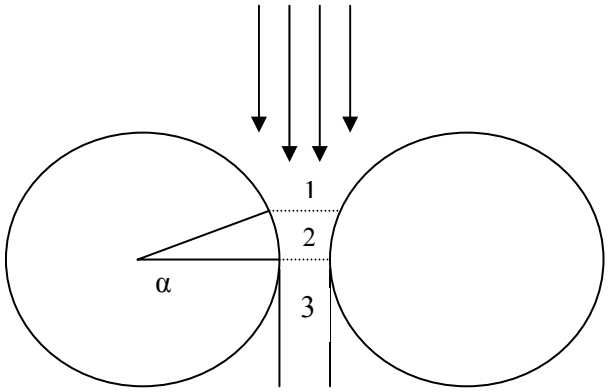

Figure 5: The three zones of the roller compactor. 1: Feeding zone; 2: Compaction zone; 3: Extrusion zone; α: The nip angle.

5.3 Compression and compaction of roller compacted granules

5.3.1 Effect of equipment variable

For pharmaceutical application of roller compaction, granules have mostly been produced for further compression into tablets. The granule quality and the tablet quality have been studied in relation to different process parameters of the roller compactor. The roll pressure, feed and tamp screw speeds and roll speed are among the most examined settings.

One of the few researchers, who studied the compressibility, was Falzone et al. (1992), examining the effect of the roll speed, the feed and tamp screws. The compressibility was determined as the densities of various tablets as a function of the compaction pressures in double logarithmic transformation. Using microcrystalline cellulose, lactose and a blend of paracetamol, microcrystalline cellulose and lactose, three different results were obtained. For microcrystalline cellulose a high horizontal feed screw speed and low roll speed were shown to

have significance for the compressibility while the lactose was affected by the interaction of the two feed screws. The compressibility of the paracetamol blend was mainly affected by the feed screw speed and roll speed interaction. These results indicate that the effect equipment parameters may depend on the material properties.

Sheskey and Dasbach (1995) varied the compaction pressure and three binder concentration (6.25, 12.5 and 25%) in a study of the application of nine commonly used polymers in a roller compacted granule of niacinamide. At low binder level, the tablet crushing force was not affected by variation in the roll pressure. However, increasing the binder level increased the tablet crushing force and decreased the tablet friability. At high binder level, low roll pressures resulted in tablets with higher mechanical strength and lower friability, indicating the change from brittle to more plastic deformation made the formulation more sensitive towards roller compaction. Similar results were obtained by Inghelbrecht and Remon (1998) when adding increasing ibuprofen (brittle) concentrations in microcrystalline cellulose (plastic) in roller compacted granules, compressed at low and high roll pressures. Thus generally, significant larger tablet crushing forces were obtained at low roll pressure for the pure microcrystalline cellulose. Adding ibuprofen, the tablet crushing force increased and the difference between the roll pressures became insignificant. Several studies of microcrystalline cellulose and other plastic deforming materials confirm the increase in tablet mechanical strength and decrease in the tablet friability as the materials is exposed to decreasing compaction pressures during dry processing of the granules (Bultmann, 2002; Weyenberg et al., 2005). On the other hand, manufacturing the granules at high compaction pressure, large granules with a large flowability and low friability are usually obtained

(Bultmann, 2002; Grulke et al., 2005; Inghelbrecht et al., 1997; Weyenberg et al., 2005).

In a predominating brittle formulation, the impact of the roll speed, feed screw speed and the roll pressure on the crushing force was concluded to be limited (Sheskey and Hendren, 1999). The difference between the tablets from direct compression and tablets from roller compaction was larger than the variation among the roller compacted granules. In a study of brittle materials consisting of calcium carbonate having different morphology and sorbitol in various sizes, the roller compaction process was demonstrated to be robust in regard to compactibility and flowability (I). Furthermore, it was concluded that the effect of the morphology and size was more influential on the compaction properties than the settings of the roller compactor including roller force, gap size, roller speed and feed and tamp auger speed. However, in a study of magnesium carbonate, which also is expected to be brittle, a decrease in tensile strength of $^1/_3$ was demonstrated when increasing the specific compaction force of the roller compactor from 1 to 7 kN/cm (Freitag and Kleinebudde, 2003). Consequently, in most cases, brittle materials are less affected by roller compaction than plastic deforming materials. This phenomenon is probably caused by the formation of new surfaces during fragmentation, enabling new interparticulate bonds.

5.3.2 Effect of material properties

Among the starting materials in roller compacted granules, differences in particle morphology and particle size in roller compacted granules have been studied in relation to the consolidation characteristics.

Freitag et al. (2004) evaluated the effect of roller compaction on the tablet characteristics of different morphology and sizes of magnesium carbonate. The particles were either described as nearly round or pin-like with a mean particle

size varying between 7.0-43.2 μm, resulting in different surface areas. The increased specific surface area of the starting material improved the tensile strength of tablets. In a similar study of roller compacted granules, compactibility and compressibility of different particle shapes of calcium carbonate (irregular, cubic and scalenohedral) and different particle sizes of sorbitol (45 –236 μm) were examined in blends (I). In general, the scalenohedral calcium carbonate and the smallest sized sorbitol, having the largest surface area, improved the compactibility and the compressibility the most for powders and granules. The calcium carbonate distribution in size fractions of the granules was examined and the demixing potential was calculating (II). The demixing potential was specified as the coefficient of variation of calcium carbonate in the different size fractions as a quantification of the latent ability to segregate (Thiel and Nguyen, 1982, II). A low demixing potential i.e. the most uniform distribution of the calcium carbonate in the size fractions was found for the scalenohedral calcium carbonate and the smallest sized sorbitol. A relationship between the demixing potential and the compactibility of the direct compressible tablets was demonstrated as the more compactible the powder blends became, the smaller became the demixing potential (II).

In a stability study of roller compacted mannitol and sorbitol of different particle sizes, the mechanical strength of tablets stored below the critical relative humidity increased immediately and stabilized over 90 days (IV). For sorbitol tablets stored above the critical relative humidity, the tablets partially dissolved after 24 hour. A smaller particle size emphasised the changes of tablet mechanical strength during storage (IV).

5.3.2 Effect of roller compaction

Several authors have reported a decrease in tablet mechanical strength of roller compacted granules in comparison to direct compression (Sheskey and Hendren, 1999; Freitag and Kleinebudde, 2003; I). Though, results have been reported where the tablet mechanical strength of roller compacted granules, consisting of 5-10% powdered cellulose in magnesium carbonate was improved considerably in comparison with the corresponding blends (Freitag et al., 2005). These findings were related to the decrease in pore size in tablets of the granules. The relative tap densities were also reduced in these granules, suggesting that decreased tablet porosity also contributed to the improved mechanical strength.

In a comparative study of similar size fractions of direct compression excipients ungranulated and granulated by slugging, a reworking potential was quantified as the area under the tensile strength/recompression pressure profile expressed as a percentage of the area under the initial compression profile (Malkowska and Khan, 1983). The loss in compactibility was explained by work hardening, defined as a materials resistance to permanent deformation and by the production of robust granules during compression since the granules have an increased resistance to deform (Malkowska and Khan, 1983). The effect of the work hardening was more evident when the slugging was performed at a higher compression pressure (Malkowska and Khan, 1983). Later, this work was criticized because the size fractions were claimed to be too wide, resulting in incomparable size distributions (Sun and Himmelsprach, 2006). As a replacement for the work hardening theory, Sun and Himmelsprach (2006) suggested a granule size enlargement hypothesis. This was based on results where size fractions had a larger impact on the tensile strength than the number of recompression in a roller compactor. However, these results were probably caused by the dominating effect of the initial size fraction of the powder rather

than the size fraction of the granules. Furthermore, the granule size enlargement hypothesis presumes the granules stay intact during compression, which is unlikely.

A novel mechanism for the loss in compactibility was suggested after studying the calcium carbonate distribution in size fractions of roller compacted granules containing sorbitol (II). The calcium carbonate distribution in the granule fractions was regarded as a product of the ability of the powders to form interparticulate bonds during roller compaction and stay attached during the grinding of the ribbons. The stronger interparticulate attractive forces of sorbitol were obvious as the sorbitol mainly existed as agglomerates whereas the smallest size fraction < 75 μm mainly consisted of calcium carbonate. Based on this observation, it was suggested that the fracturing of the ribbon mainly occurred at the weakest interparticulate bonds (the calcium carbonate: calcium carbonate bonds) and thus only the strongest bonds resisted the force of the granulator. Consequently, roller compacted granules are covered with the weakest bonding area on the granule surface. Therefore, fracturing of a tablet of roller compacted granules will occur between the granules in weak bonding zones, facilitating a much easier fracturing than if the weakest bonding areas were uniform distributed all over the tablet.

Only in few papers, the compressibility has been discussed for roller compacted granules. The compressibility, quantified as the apparent mean yield pressure (Freitag and Kleinebudde, 2004) and the Walker coefficient (I), was decreased by roller compaction. Further, the Walker coefficient for tablets of roller compacted granules was considerably smaller than tablets manufactured from wet processed granules (III). This difference was explained as the roller compacted granules were softer and denser, resulting in a shorter compaction

time and lower in-die volume during compression; accordingly the dry processed granules obtained lower compressibility (III).

6. Conclusion

The Walker coefficient appeared to be suitable for characterizing the compressibility of calcium carbonate and sorbitol due to its curve-fitting abilities and good discrimination powder. The compactibility was successfully quantified as the slope of the specific crushing strength versus the compaction pressure in the linear region of the pressure profile.

The roller compaction process was demonstrated to be robust and stable in regard to the compactibility of the brittle materials calcium carbonate and sorbitol. In fact, the morphology of the calcium carbonate and the sorbitol particle size were more influential on the compaction properties than the settings of the roller compactor. By adding decreasing sizes of sorbitol to the calcium carbonate, the compressibility and the compactibility were improved considerably.

In comparison to the corresponding direct compressible blends, the compaction properties of the dry granules were decreased significant. It is hypotized that the roller compacted granules are covered with the weakest bonding area on the granule surface as a result of the grinding process which splits the ribbon in the weakest links. The fracturing of a tablet of roller compacted granules will therefore occur between the granules in weak bonding zones. This fracturing is facilitated much easier than if the weakest bonding areas were uniform distributed as it is expected to be in a tablet made from direct compression.

Comparing wet processed granules to roller compacted granules, a much higher compressibility and compactibility was obtained. Further, an overall relationship between the compressibility and compactibilty for powders, dry granulated materials and wet granulated materials was obtained.

7. Perspectives

From an industrial point of view, an easy preliminary test could be useful for predicting the granule and tablet properties of a formulation at a tablet press without having to do slugging and with a minimum quantity of starting material. Often, researchers only have access to production scale roller compactors, which requires a 5-10 kg powder blend. In this context, it is most likely that the compactibility of a powder material can be applied for predicting the ability to form granules with a small amount of fines.

Further investigations of the mechanism for explaining the loss in compactibility for roller compacted granules could be performed, applying powders in different colours for visualising the demixing behaviour. Performing content uniformity measurements of tablets manufactured from roller compacted granules, having a large demixing potential, could be relevant in order to clarify whether a demixng actually will occur.

Based on the theory for explaining the loss in compactibility (II), it seems likely that roller compacted granules of minimum two starting materials, are formed from a core substance covered with powder having the weakest ability to form interparticulate bonds. In further investigations, it could interesting to examine whether roller compaction could be utilized for coating of particles in order to

control the release or protect a compound from other substances in a formulation.

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